REMARKS

Claim 14 has been amended. Claims 16-18 were previously withdrawn. Claims 22-42 were previously cancelled without prejudice or disclaimer. Subsequent to the entry of the present amendment, claims 14-15 and 19-21 are pending and at issue. These amendments and additions add no new matter as the claim language is fully supported by the specification and original claims.

Applicants and Applicants' representatives gratefully acknowledge the careful consideration of the application by the Examiner in the telephone interview held on July 20, 2005, wherein Applicants' representative provisionally elected Group II (claims 14-15 and 19-21) for examination. Although Applicants traverse the requirement for the reasons set forth below, the election of Group II has been made in order to be fully responsive to the Restriction Requirement.

I. Amendment to the Specification and the Claims

The Title and Abstract of the specification have been amended. The new Title reflects the claimed invention, and the new Abstract recites a method of using GDF-7 antibodies. The amendments are fully supported in the specification and claims as originally filed. Hence, no new matter has been added.

Claim 14 has been amended to recite:

> A method of detecting Growth Differentiation Factor-7 (GDF-7) in a sample comprising:
> contacting the sample with a substantially pure antibody, or an antigen binding fragment thereof, that specifically binds to a GDF-7 polypeptide as set forth in SEQ ID NO: 6, and
> detecting the binding of the GDF-7 antibody, thereby detecting GDF-7 in the sample.

The amendments to claim 14 is fully supported in the specification and claims as originally filed. For example, the phrase "GDF-7 in a sample" is supported on page 14, lines 6-16 and page 24, lines 11-14 and FIG. 1 (or paragraph [0038], [0071] of 20070127696); and the phrase "antigen

binding fragment thereof" is supported on page 13, lines 15-24 (or paragraph [0036] of 20070127696). Hence, the amendments do not add any new matter.

II. Restriction requirement

Claims 14-21 are pending. The Office alleges that the claims are directed to two (2) distinct and independent inventions as follows: Group I (claims 14-17) drawn to a method for detecting a cell proliferative disorder *in vivo* using GDF-7 antibody; and Group II (claims 14-15 and 19-21) drawn to a method for detecting a cell proliferative disorder *in vitro* using GDF-7 antibody.

Applicants traverse the Restriction Requirement for the reasons stated below. However, in order to be fully responsive, Applicants elect the claims of Group II, claims 14-15 and 19-21, directed to a method of a method for detecting a cell proliferative disorder *in vitro* using GDF-7 antibody. Applicants reserve the right to pursue prosecution of the non-elected claims in a later filed application claiming the benefit of priority of the above-identified Application.

Applicants traverse the restriction requirement with respect to the division of the claims of Group I from the claims of Groups II. It is submitted that a thorough search of the elected claims of Group I will include art relevant to the claims of non-elected Group II. Further, that that search and examination of the all claims 14-21 does not pose a serious burden to the Examiner. In particular, a thorough search with regard to the method of detecting a cell proliferative disorder *in vitro* or *in vivo* using GDF-7 antibodies would be relevant to both Groups and not just Group I. That is, the only difference between the methods of Group I and the methods of Group II, is whether they are performed in an artificial environment (*in vitro*) or in the living body (*in vivo*). Hence, this would constitute of waste of U.S. Patent and Trademark Resources by requiring duplicative searches.

Accordingly, it is respectfully requested that the division of the claims of Group I and Group II be reconsidered, and that the Examiner rejoin and examine claims 14-17 (Group II) with elected claims 14-15 and 19-21 (Group II).

III. Rejections under 35 U.S.C. §101 (utility)

Claims 14-15 and 19-21 are rejected as allegedly lacking a patentable utility, as required under 35 U.S.C. § 101. Applicants respectfully traverse the rejection as it may apply to the amended claims.

According to the Office Action the instant application does not disclose the biological role of GDF-7 and its significance (see page 4 of the Office Action). The Office Action also alleges that even though GDF-7 has structural homology to other members of the TGF-beta family of proteins, utility and function of other TGF-beta proteins cannot be attributed to GDF-7 by analogy (paragraph bridging pages 4 and 5; page 7). The Office Action finds further support for this position in Sklonick (2000), which states that knowledge of the overall structure or domain family is not enough to assign function to a protein (page 8, last paragraph). The Office Action also alleges that there is no utility because Applicants' failure to describe the differential expression of mRNA encoding GDF-7 is a failure to provide a standard from which to show that a change in expression of the protein is associated with a disease or condition (page 5, last paragraph; and page 6, second paragraph). Thus, according to the Office Action, there is allegedly no nexus between the claimed antibody to GDF-7 and to the recited disorders (page 6, third paragraph); and therefore, there is allegedly no "real world" or "credible" use for the claimed antibody to GDF-7. However, the Office Action admits that only *one* substantial credible utility is required (page 8, second paragraph).

Applicants respectfully traverse each of the above allegations as discussed in more detail below. It is noted, that because the Office Action refers to pages and line numbers of the application as filed (or to PCT/US94/07799), even though the instant application has been published as Publication 20040127696, Applicants will also refer to pages and line numbers based on the PCT/US94/07799 application.

First, as an initial matter, it is noted that U.S. Patent No. 5,986,058, which contains claims directed to the GDF-7 polynucleotide and the encoding a GDF-7 polypeptide, and U.S. Patent No. 6,680,372, which contains claims directed to the GDF-7 antibody, have issued from the same priority application of the subject application. It is well recognized that a patent shall be presumed valid (35 U.S.C. § 282), and that this presumption of validity applies to utility (*Raytheon Co. v. Roper Corp.*, 220 U.S.P.Q. 592, 599 at fn. 7, Fed. Cir. 1983), as well as to novelty and non-obviousness. Hence, issuance of the above-identified patents provides *prima facie* evidence that a GDF-7 polypeptide, the encoding polynucleotide and the antibody have patentable and "credible" utilities.

The Office Action's alleges that the utility and function of other related TGF-beta proteins cannot be attributed to the claimed antibody to GDF-7, yet, it is well established that Courts have routinely found evidence of structural similarity to a compound known to have a particular therapeutic or pharmacological utility as being supportive of an assertion of therapeutic utility for a new compound. In *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980). In *In re Jolles*:

> The claimed compounds were found to have utility based on a finding of a close structural relationship to daunorubicin and doxorubicin and shared pharmacological activity with those compounds, both of which were known to be useful in cancer chemotherapy. ... Office personnel should evaluate not only the existence of the structural relationship, but also the reasoning used by the applicant or a declarant to explain why that structural similarity is believed to be relevant to the applicant's assertion of utility.

The instant application is analogous to that described in *In re Jolles*, because the instant application discloses that GDF-7 shares structural homology with members of the TGF-beta family (see also FIG. 1 and 4):

> The TGF-beta superfamily consists of multifunctional polypeptides that control proliferation, differentiation, and other functions in many cell types. Many of the

> peptides have regulatory, both positive and negative, effects on other peptide growth factors. The structural homology between the GDF-7 protein of this invention and the members of the TGF-beta family, indicates that GDF-7 is a new member of the family of growth and differentiation factors. Based on the known activities of many of the other members, it can be expected that GDF-7 will also possess biological activities that will make it useful as a diagnostic and therapeutic reagent (page 5, lines 9-17; or paragraph [0014] of 20040127696).
>
> Several members of the TGF-beta superfamily possess activities suggesting possible applications for the treatment of cell proliferative disorders, such as cancer. In particular, TGF-beta has been shown to be potent growth inhibitor for a variety of cell types (Massague, Cell, 49:437, 1987), MIS has been shown to inhibit the growth of human endometrial carcinoma tumors in nude mice (Donahoe, et al, Ann. Surg., 194:472, 1981), and inhibin alpha has been shown to suppress the development of tumors both in the ovary and in the testis (Matzuk, et al., Nature, 360:313, 1992). GDF-7 may have a similar activity and may therefore be useful as an anti-proliferative agent, such as for the treatment of tumors of neural origin. (page 6, lines 10-19; or see paragraph [0016] of 20040127696).

Hence, the shared structural homology of GDF-7 with other TGF-beta proteins is indicative of shared function with other TGF-beta proteins. Thus, in view of the specification and the state of the art at the time the subject application was filed or to which subject application claims priority to (i.e. July 7, 1994, the International filing date of PCT/US94/07799), it is submitted that one skilled in the art reasonably would have believed that GDF-7, had a role in differentiation and embryonic development which was characteristic of the TGF-beta family of proteins.

Also, according to the Office Action, there is allegedly no standard from which to compare the expression of GDF-7 in a disease versus that in normal tissue because Applicants' have failed to describe the differential expression of mRNA encoding GDF-7 or change in expression of the protein associated with a disease or condition (page 5, last paragraph and page 6, second paragraph of the Office Action). It is submitted, that differential expression of GDF-7 has been shown and that there is a "nexus" or "reasonable correlation" between using the GDF-7 antibody as a diagnostic and research tool to detect a cell proliferative disorder.

For example, GDF-7 is differentially expressed in fetal and neonatal brain and in the Neuro 2A neuroblastoma cell line (Example 2 at page 24). It is well known that an amount of a protein produced by particular cells, including the amount of GDF-7 produced by neural cells as disclosed in the subject application, can be directly related to the number of cells producing the protein, and, it is submitted, is a well established utility that a determination of the levels of such proteins can be diagnostic of a particular tissue containing cells that produce the protein. As such, one of skill in the art would recognize in light of the present specification that measuring changes in GDF-7 has a credible real world utility as a marker for function of neural cells. Thus, a skilled artisan would understand that there is a "nexus" between changes in proliferation of neural cells, due to, for example, a neural disorder, and a corresponding change in GDF-7 level, as detected using an anti-GDF-7-antibody.

Also, according to the Office Action, Sklonick et al. (2000) states that functional information can only be derived from structural information to a limited extent (page 286, column 1). Sklonick et al. (2000) also state that the "overall structure or domain family is still not enough to confidently assign function (page 286, column 1)." However, Applicants' submit that as a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *Nelson v. Bowler*, 626 F.2d 853, 206 USPQ 881 (CCPA 1980). See MPEP § 2107.03.

> The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of *statistical certainty*, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a *reasonable correlation between the activity and the asserted use* (emphasis added). *Nelson v. Bowler*, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980). See MPEP § 2107.03.

Further, Lee K.J. et al. (1998) disclose that GDF-7 has a regulatory effect on other peptide growth factors (e.g., bone morphogenetic factors) as originally described in the instant application (page 5, lines 9-12). Lee K.J. et al. (1998), "Neuronal patterning by BMPs: a requirement for GDF-7 in the generation of discrete class of commissural interneurons in the mouse spinal cord," *Genes & Development*, 12:3394-07 (Exhibit A). Lee et al. (1998) describe that GDF-7 mRNA is expressed in the neonate brain (page 3395, col. 2, Results section) and that GDF-7 homozygous mutant animals developed severe hydrocephalus (FIG. 3F-I) after about 14 to 21 days after birth (postnatal). Hence, Lee et al. (1998) support that which was originally disclosed in the instant application in that it confirms that the structural homology of GDF-7 to other TGF-beta proteins (e.g., BMPs) *is* indicative that GDF-7 has similar function to other TGF-beta proteins (e.g., regulatory effect on other peptide growth factors such as BMPs).

It is submitted that there is a "reasonable correlation" between GDF-7 activity and its asserted claimed use. For example, the anti-GDF-7 antibody as disclosed in the subject application is useful as a research tool, including as a diagnostic reagent to detect a cell proliferative disorder, e.g., a GDF-7 associated disorder (page 14, lines 6-16). The specification describes various uses of the claimed anti-GDF-7 antibody e.g., immunodiagnosis, immunotherapy, competitive and non-competitive immunoassays, RIA, sandwich immunometric assay, immunohistochemical assays and the like (page 14, lines 17-28; or paragraph [0039] of 20040127696). Thus, Applicants submit that a research tool clearly is a patentable utility.

In summary, it is submitted that the use of the GDF-7 antibody to determine the level of a protein, wherein the level of the protein is diagnostic of the proliferative state of cells that produce the protein, is a specific, substantial and well established utility, and that, in view of the subject application, one skilled in the art clearly would have recognized that an anti-GDF-7 antibody can be used to determine levels of GDF-7, which can be indicative of a cell

proliferative disorder. Therefore, a substantial credible utility has been described in the application as filed.

Accordingly, withdrawal of rejection of claims 14-15 and 19-21 under 35 U.S.C. § 101 is respectfully requested.

IV. Rejections under 35 U.S.C. §112, First Paragraph (enablement)

Claims 14-15 and 19-21 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one of skill in the art to make or use the invention. The objection to the specification and corresponding rejection of claims 14-15 and 19-21 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement are respectfully traversed.

For the reasons set forth above, it is submitted that the specification discloses a patentable utility, and it is further submitted that the specification discloses methods using anti-GDF-7 antibody for purposes of practicing the claimed methods (e.g., Example 2). As such, it is respectfully requested that this objection to the specification be withdrawn and that the corresponding rejection of the claims under 35 U.S.C. § 112, first paragraph, be removed.

Accordingly, withdrawal of rejection of claims 14-15 and 19-21 under 35 U.S.C. § 112, first paragraph is respectfully requested.

V. Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 14-15 and 19-21 are rejected under 35 U.S.C. § 112, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant traverses this rejection as it may apply to the amended claim.

According to the Office Action, claim 14 is allegedly vague and indefinite for reciting the phrases (page 11 of the Office Action): "cell proliferative disorder" because it refers to malignant and non-malignant cells; "a fragment thereof" because there are no metes and bounds and such a term can allegedly encompass one amino acid; "a subject suspected of having GDF-7 associated disorder" because it is unclear what the "suspect cells" would be; and that claim 14 fails to recite steps.

Claim 14 has been amended to recite:

A method of detecting Growth Differentiation Factor-7 (GDF-7) in a sample comprising:
contacting the sample with a substantially pure antibody, or an antigen binding fragment thereof, that specifically binds to a GDF-7 polypeptide as set forth in SEQ ID NO: 6, and
detecting the binding of the GDF-7 antibody, thereby detecting GDF-7 in the sample.

Support for the amendments to claim 14 are discussed above. The rejection with regards to the phrase "cell proliferative disorder" and "a subject suspected of having a GDF-7 associated disorder" are moot as the claim has been amended. The phrase, "a fragment thereof" has been limited to "an antigen binding fragment thereof", which is understood by one skilled in the art to encompass an antibody to the GDF-7 polypeptide as well as any GDF-7 antibody fragment which binds to a GDF-7 antigen or epitope. This is described in the specification, for example, see page 13, lines 15-24 and page 14, lines 6-16). Further, the method recites the steps of "contacting" and "detecting" which are sufficient for "detecting GDF-7 in the sample". Thus, it is submitted that claim 14 clearly recites the metes and bounds of the claimed invention. It is further submitted that claims 15 and 19-21 are not vague and indefinite, in so far as they are dependent upon claim 14, which has been amended to improve its form.

Accordingly, withdrawal of rejection of claims 14-15 and 19-21 under 35 U.S.C. § 112, second paragraph is respectfully requested.

Conclusion

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

Applicants do not believe any other fees are due in connection with this submission, however if any other fees are due, please charge any fees, or make any credits, to Deposit Account No. 07-1896.

Respectfully submitted,

Date: November 18, 2005

Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

DLA PIPER RUDNICK GRAY CARY US LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer No. 28213